A review of distribution of atherosclerosis in the lower limb arteries of patients with diabetes mellitus and peripheral vascular disease

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The Distribution of Atherosclerosis in the Lower Limb Arteries of Patients with Diabetes Mellitus and Peripheral Vascular Disease: A systematic review

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Abstract

Objective: There is a generally accepted hypothesis that patients with diabetes mellitus (DM) have a higher burden of atherosclerotic disease below the knee compared to patients without DM (NDM). The aim of this review was to summarize the evidence regarding this hypothesis.

Methods: The literature was searched for papers that compared the anatomical distribution of atherosclerotic disease in patients with DM and those without using radiological imaging. Search terms used included "diabetes mellitus", "peripheral vascular disease", 'distribution of disease", "angiography", "computed tomography angiography" and "magnetic resonance angiography". Where possible, the number of patients with disease in each arterial segment was extracted and included in a forest plot. A descriptive approach was taken when this was not possible or a scoring system was used.

Results: Fourteen studies were included in the review and it was possible to summarise data from nine of these in a forest plot. Fifteen different arterial segments were described, however, the most commonly used segments that differentiated between proximal and distal disease were aorto-iliac (A-I) (DM=466 patients, NDM=458), femoro-popliteal (F-P) (DM=568, NDM=585), tibial (DM=306, NDM=417). The resulting forest plot showed that those with DM were significantly less likely to have disease in the A-I segment (OR 0.25 (0.15-0.42)) and significantly more likely to have disease in the tibial segment (OR 1.94 (1.27-2.96)). In the DM group, there was a trend towards relative sparing in the F-P segment but this does not reach significance (0.66 (0.33-1.31)).

Conclusions: These results support the hypothesis that patients with DM are more likely to have atherosclerotic disease in the tibial vessels than patients without DM. There is however limited information on how individual vessels are affected. Further information on

this and a greater understanding of why the distal vessels are more affected are avenues for future research.

Introduction

Infra-popliteal disease is associated with critical limb ischaemia which is the final stage in the disease course of peripheral arterial disease (PAD)[1]. The pattern of vascular disease influences the options there are for revascularisation. Management of distal disease is more challenging than proximal disease, although advances in this area are being made[2-5]. Despite these advances patients with distal disease have a higher risk of an amputation and shorter amputation-free survival[6].

The prevalence of diabetes mellitus (DM) is increasing worldwide and is a major risk factor for PAD[7,8]. Patients with DM have a predisposition towards a higher burden of atherosclerotic disease below the knee compared to patients without DM (NDM). This is considered to have an impact on both the treatment options available and prognosis following revascularisation in patients with DM[9,10].

This hypothesis of a higher burden of disease in the tibial arteries is widely accepted within the medical community. The aim of this review was to summarise the quality of the evidence supporting this hypothesis.

Methods

A literature search was performed using the search terms “diabetes mellitus”, “peripheral vascular disease”, ‘distribution of disease”, “angiography”, “computed tomography angiography" and "magnetic resonance angiography". Synonyms and various combinations were used in the search strategy which involved both MESH and keyword searches. Embase and MEDLINE databases were searched including papers published from 1946 to present day and in-process citations. References from relevant studies were also scrutinised for potential studies.

Papers were included if arterial imaging of the lower limb was undertaken using digital subtraction angiography (DSA), Computed Tomography Angiography, or Magnetic Resonance Angiography. They were excluded if the indication for imaging was not PAD, if there was no separation of patients with and without DM or only patients with DM were included. The final requirement was an anatomical description of the arteries affected by atherosclerotic disease. This description could be given using a scoring system or proportions of arterial segments affected.

Statistical analysis

For papers that included proportions of patients with PAD by arterial segment the number of patients who had disease in each arterial segment was extracted by one author (DL). These papers were included in a forest plot that was produced using Revman 5.3 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.). Data were summarised as odds ratio (OR) with 95% confidence intervals.

Results

From the literature search, 151 potential papers were identified and following review of titles, abstracts, full text and references 14 studies were included in the review (Figure 1).

The papers dated from 1964 to 2009 and were all cross-sectional studies apart from one cohort study[11] and two case-control studys[12,13]. The majority of papers did not state if their analysis was by patient or by limb, in most, it appeared that a single treated limb was included per patient[11,13-18]. Four papers included all treated limbs[19-22], one paper included both legs for all patients[12], one paper analysed by lesion[23] and one paper only used the data from the left leg if there was bilateral imaging as they found the legs to be comparable[24]. How risk factors for PAD were treated varied between papers. Four papers performed some form of multivariate analysis to stratify for risk factors[12,18,22,23], the majority of remaining papers reported proportions of risk factors and comparability between groups however two papers made no mention of risk factors[14,19]. No studies considered type I and type II DM separately. One paper found a significant difference in the proportion of men and women in their cohorts[12] and one paper found significant differences in the proportions of smokers[20]. Most papers had cohorts with a mean age in the mid-sixties although two papers deliberately selected young cohorts[14,15] and two papers had older cohorts[11,21]. The majority of cohorts consisted of approximately 60% men apart from Ozkan *et al* who had 85.9% men[18]. The proportion of smokers in each group ranged from 13.5% to 83.2% (Table 1).

All the studies used angiography to visualise the arterial tree and in total 15 different arterial segments were described (Table 2). The most commonly used segments that differentiated between proximal and distal disease were aorto-iliac (A-I), femoro-popliteal (F-P), tibial (Tib). Seven studies also included a category that represented disease at multiple levels (ML). These segments were included in the forest plot along with smaller segments that fitted in the same group. I.e. patients with disease in the popliteal artery could be included in the F-P group but those in a popliteal/tibial group could not be included. The description of what constituted significant disease varied between papers. Of the papers that described proportions of arterial segment involved five only included occlusions[14,17,19-21], two defined a significant stenosis as involving more than 20% of the lumen[15,16], two defined it as more than 50%[12,18] and in one paper the definition was not stated[23].

Proportions of arterial segments affected

Ten studies described the proportions of arterial segments affected by PAD and included 1682 patients with DM and 2775 without DM[12,14-16,18-21,23,25]. For two papers it was not possible to extract sufficient data[18,23] they were not included in the analysis but their results will be discussed.

The resulting forest plot (**Error! Reference source not found.**~~Figure 2~~) demonstrates that those with DM were significantly less likely to have disease in the aorto-iliac segment (OR 0.25 (0.15-0.42), n=DM 466/NDM 458) and significantly more likely to have disease in the tibial segment (OR 1.94 (1.27-2.96), n=DM 306/NDM 417). In the DM group, there is a trend towards relative sparing in the femoro-popliteal segment but this does not reach significance (0.66 (0.33-1.31), n=DM 568/NDM 585). There is also a suggestion that those with DM were more likely to have multilevel disease, again this does not reach significance (1.26 (0.93-1.70), n=DM 549/NDM 557).

The two papers not included in the meta-analysis showed a similar pattern. Diehm *et al*[23], in a retrospective cohort that examined the risk factors for distribution pattern of lower limb atherosclerosis in 2659 patients (891 with DM), on multivariate logistic regression found that DM had a relative risk ratio of 0.59 (0.49-0.72, p<.001) for iliac disease compared to 1.68 (1.47-1.92, p<.001) for tibial disease. Ozkan *et al*[18] performed a similar analysis in 626 patients with symptomatic PAD 261 of whom had DM. They found on univariate analysis the presence of DM was related to odds ratios of 0.56 (p=.001) for aorto-iliac disease, 1.16 (p=.39) for femoro-popliteal disease and 2.44 (p=.001) for tibial disease.

Scores to describe distribution of disease

Four papers reported scores by arterial segment[11,13,22,24]. Three of these used the Bollinger score[26] and one[22] a score described by LaMorte *et al* in 1985[27]. Briefly, Bollinger's score is a semi-quantitative score that considers each arterial segment separately. Each arterial segment is assessed for the presence of plaques less than 25% of the lumen, stenoses less than 50% of the lumen, stenoses more than 50% of the lumen and occlusions. A higher score is achieved if these lesions are multiple and involve more than half the length of the segment. The minimum score is zero and maximum fifteen (occlusion for more than half the length). The scoring matrix used for each segment individually is shown in Table 3. LaMorte *et al*'s score assigns a score of zero to a non-visualised vessel, one to a partially compromised vessel and two to an intact vessel. By applying this score to 227 patients with PAD, Menzoian *et al* demonstrated significantly lower scores (i.e. more disease) in the posterior tibial artery (PTA) (0.51 vs 1.02, p<.05) and peroneal artery (PEA) (0.9 vs 1.28, p<.05) as well as the sum of the tibial vessels (2.17 vs 3.13, p<.05) in the DM group [22].

Despite all using the Bollinger score it is hard to compare the results for Jude *et al*, van der Feen *et al* and Diehm *et al* due to the different vessels reported. Jude *et al* used the segments originally described by Bollinger (ten arterial segments (per leg) from the infra-renal aorta down to the proximal 3cm of the anterior tibial artery (ATA) and the proximal 5cm of the PTA and PEA[26]) and reported the median score for each segment. In 136 patients they found those in the DM group (n=58) had a significantly higher score in the profunda femoris (mean score 3 (IQR 0-5) vs 0 (0-2)), popliteal (7 (3-10) vs 3 (0-4)), ATA (13 (4-15) vs 3

(0-4)), PTA (15 (0-15) vs 4 (0-14)) and PEA(5 (0-5) vs 0 (0-6))[24]. Van der Feen *et al* also used the original description of the segments but did not report the individual scores for each segment. Instead, the scores were combined to form the "upper leg" (aorta, iliacs, profunda femoris and SFA) and "lower leg" (popliteal, ATA, PEA, and PTA). In 37 patients with DM matched for age gender and smoking to 37 patients without DM, there was a higher mean score for the lower leg in the DM group but this was not significant (47.4 vs 37.6, p=.22). While the scores for the individual segments were not reported, the included bar graphs show that the only segment with a significant difference was the PEA in the right legs ($p<0.05$), those in the DM group had a higher score[13]. Diehm *et al* only scored the below the knee segments including the plantar vessels and so extended Bollinger's original description. Their patient groups were patients with DM (n=25), patients with renal insufficiency (n=15), patients with both DM and renal insufficiency (n=25) and 25 controls with neither DM or renal insufficiency. They found no significant difference between the groups although those in the DM group and in the renal insufficiency group tended towards higher scores.

Discussion

These results demonstrate that there is a difference in the distribution of atherosclerotic disease in patients with DM compared to those without. The hypothesis that patients with DM have more disease below the knee is supported. Patients with DM are less likely to have disease in the aorto-iliac segment and more likely to have disease in the tibial segment. This is demonstrated in the forest plot, the papers that applied scores, and also the papers that it was not possible to include in the meta-analysis. In the femoro-popliteal segment, the trend is towards those without DM having more disease, although this does not reach significance. There was a trend towards multi-level disease being more common in patients with DM. Four papers assessed the severity of disease in individual vessels rather than segments[11,22,24] although only Jude *et al* did for both above and below knee vessels [24]. In patients with and without DM, the least affected of the tibial vessels was consistently the PEA.

The PEA as a target vessel for revascularisation has been considered to have limitations due to success relying on indirect collateralisation to supply the forefoot[28]. The patency of the PEA has also been demonstrated to be less critical in preventing amputation[29]. The angiosome model holds that the areas supplied by the PEA are the anterior and lateral ankle and plantar heel[30]. However increasingly the PEA has been shown to have multiple collaterals and to commonly supply the pedal arteries and as such has comparable outcomes for both surgical and endovascular revascularisation compared to other distal target vessels[31-34].

DM is known to have an impact on both the presentation of PAD and outcomes following revascularisation[35,36]. The distribution of atherosclerotic disease has also been shown to be related to outcomes following revascularisation procedures in patients both with and without DM[37]. The pathophysiology behind why patients with DM have increased PAD is complex but thought to be related to a combination of down-regulation of nitric oxide and prostacyclin, upregulation of vasoconstrictors, apoptosis of endothelial cells, activated coagulation, abnormal platelet activation and propensity towards plaque rupture[38]. There is not any clear evidence why the distal vessels are predominantly affected and while these results support the hypothesis that patients with DM have a more significant disease burden below the knee they provide us with limited information on the degree to which individual vessels or areas of vessels are affected.

A strength of the review is that all the papers used DSA as the imaging modality. DSA remains the gold standard for imaging of the lower limbs and describing the anatomic distribution of stenotic disease[39]. In the meta-analysis, there was low heterogeneity between the papers apart from those considering the femoro-popliteal segment (I^2=68%). A major weakness of the review is the low quality of the papers included. They are all observational studies, predominantly retrospective and so the body of evidence is low to very low quality[40]. An attempt to assess the methodological quality of the papers using the Newcastle-Ottawa scale[41] was made. However, all but three papers were cross-sectional studies making it not possible to apply the scale. There was consistency in the type of patients selected with the majority of papers including patients with Fontaine II to IV disease. However, one paper only included patients with intermittent claudication[18], two papers excluded those with intermittent claudication[21,25] and three papers did not define the patient group beyond symptomatic PAD[15,19,20]. As described in the results section there was also variance in how significant disease was defined. Within each paper the demographics for each group, when reported, were comparable (Table 1).

Additional weaknesses include that the papers are all relatively historical (earliest 1964, latest 2009) and the variety in how the arterial segments were described and grouped together. This grouping meant some data was not able to be included in the meta-analysis because the segment crossed the knee, weakening the data included. During data collection, it was considered that improvements in the medical management of DM and PAD may have had an impact on the distribution of disease. Evidence from high-quality randomised controlled trials on the importance of tight blood glucose control in relation to the complications of DM was published in the late nineties[42,43]. When studies from prior to the year 2000 were excluded from the meta-analysis the trends remained the same although the odds ratio for tibial disease was no longer significant (OR 1.99 (0.94-4.24)). This may suggest that optimising medical therapy has an impact on the degree of tibial disease. This review was not designed to consider this question and so firm conclusions cannot be drawn.

Conclusions

Patients with DM are more likely to have atherosclerotic disease in the tibial vessels compared to patients without. The current published evidence supports this hypothesis. There is very limited data on the degree to which individual vessels are affected. Further information on this and a greater understanding of why the distal vessels are more affected are avenues for future research. Studies that examine the impact of medical therapy on the distribution of disease may also be valuable.

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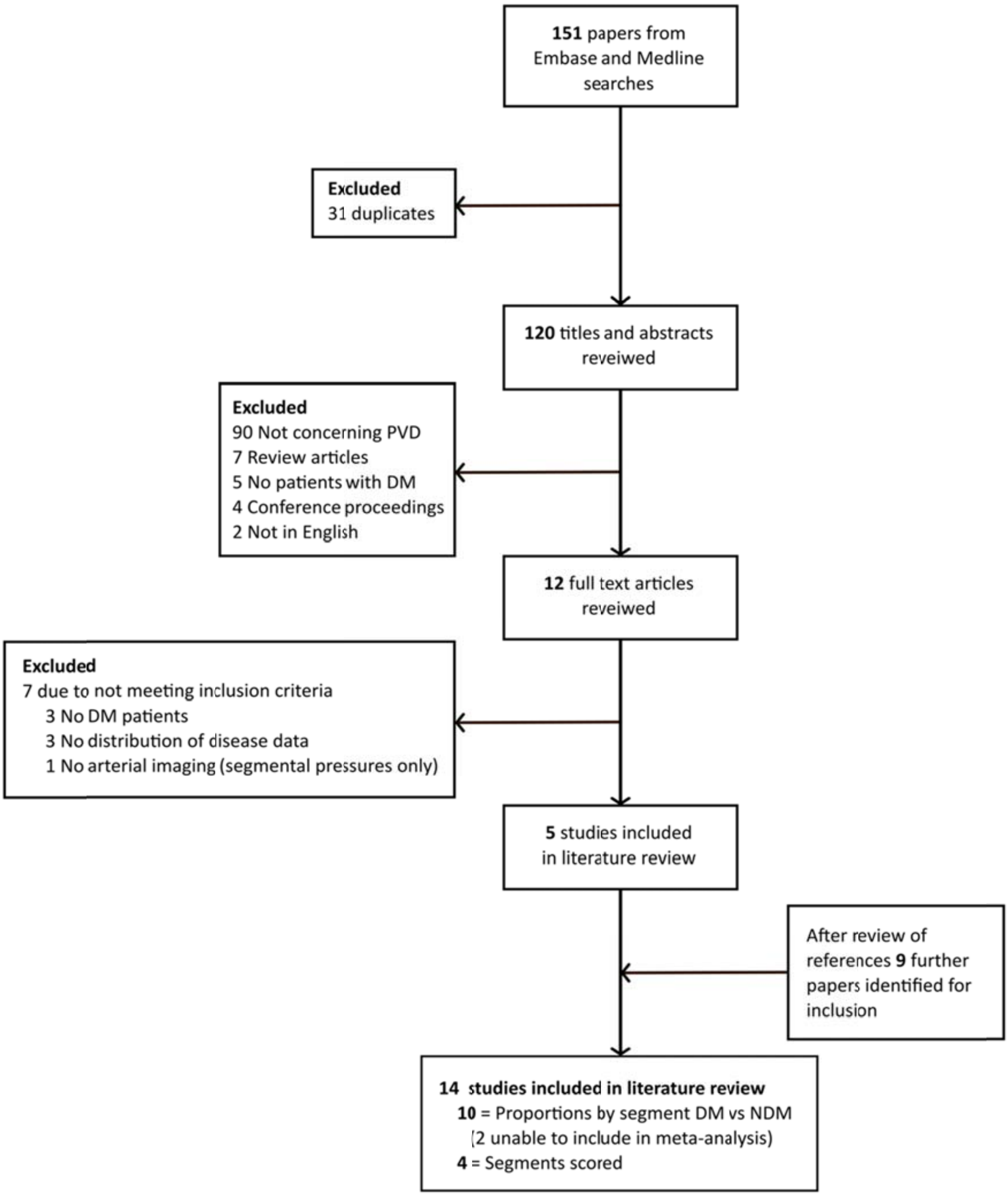

Figure 1: Inclusion flow chart

Study or Subgroup	Diabetes Events	Diabetes Total	No Diabetes Events	No Diabetes Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Aorto-iliac							
De Bakey	3	6	22	41	9.8%	0.86 [0.16, 4.79]	1964
Ciavarella	3	89	14	61	17.1%	0.12 [0.03, 0.43]	1993
Hansen	5	22	20	37	20.4%	0.25 [0.08, 0.82]	1995
Kroger	1	46	16	86	6.8%	0.10 [0.01, 0.76]	2000
Haltmayer	5	41	18	65	24.6%	0.36 [0.12, 1.07]	2001
Rueda	4	262	11	168	21.3%	0.22 [0.07, 0.71]	2008
Subtotal (95% CI)		**466**		**458**	**100.0%**	**0.25 [0.15, 0.42]**	
Total events	21		101				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.68$, df = 5 (P = 0.46); $I^2 = 0\%$							
Test for overall effect: Z = 5.09 (P < 0.00001)							
Femoro-popliteal							
De Bakey	0	6	1	41	3.6%	2.08 [0.08, 56.65]	1964
Haimovici	3	91	14	98	12.7%	0.20 [0.06, 0.74]	1967
Ciavarella	11	89	22	61	17.3%	0.25 [0.11, 0.57]	1993
Kroger	20	46	25	86	18.0%	1.88 [0.89, 3.96]	2000
Haltmayer	29	41	53	65	16.2%	0.55 [0.22, 1.37]	2001
Lazaris	19	33	43	66	16.9%	0.73 [0.31, 1.71]	2004
Rueda	12	262	6	168	15.4%	1.30 [0.48, 3.52]	2008
Subtotal (95% CI)		**568**		**585**	**100.0%**	**0.66 [0.33, 1.31]**	
Total events	94		164				
Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = 18.50$, df = 6 (P = 0.005); $I^2 = 68\%$							
Test for overall effect: Z = 1.19 (P = 0.24)							
Tibial							
De Bakey	0	6	4	41	1.9%	0.64 [0.03, 13.38]	1964
Haimovici	27	91	23	98	28.6%	1.38 [0.72, 2.63]	1967
Ciavarella	43	89	15	61	24.9%	2.87 [1.40, 5.87]	1993
Kroger	11	46	14	86	18.0%	1.62 [0.67, 3.92]	2000
Haltmayer	17	41	10	65	17.0%	3.90 [1.56, 9.74]	2001
Lazaris	4	33	8	66	9.6%	1.00 [0.28, 3.60]	2004
Subtotal (95% CI)		**306**		**417**	**100.0%**	**1.94 [1.27, 2.96]**	
Total events	102		74				
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 6.15$, df = 5 (P = 0.29); $I^2 = 19\%$							
Test for overall effect: Z = 3.09 (P = 0.002)							
Multilevel							
De Bakey	3	6	9	41	2.9%	3.56 [0.61, 20.73]	1964
Haimovici	58	91	52	98	26.3%	1.55 [0.87, 2.79]	1967
Ciavarella	36	89	24	61	20.2%	1.05 [0.54, 2.04]	1993
Hansen	5	22	8	37	5.6%	1.07 [0.30, 3.79]	1995
Kroger	14	46	31	86	15.2%	0.78 [0.36, 1.67]	2000
Lazaris	13	33	25	66	12.2%	1.07 [0.45, 2.51]	2004
Rueda	246	262	151	168	17.6%	1.73 [0.85, 3.53]	2008
Subtotal (95% CI)		**549**		**557**	**100.0%**	**1.26 [0.93, 1.70]**	
Total events	375		300				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.64$, df = 6 (P = 0.59); $I^2 = 0\%$							
Test for overall effect: Z = 1.52 (P = 0.13)							

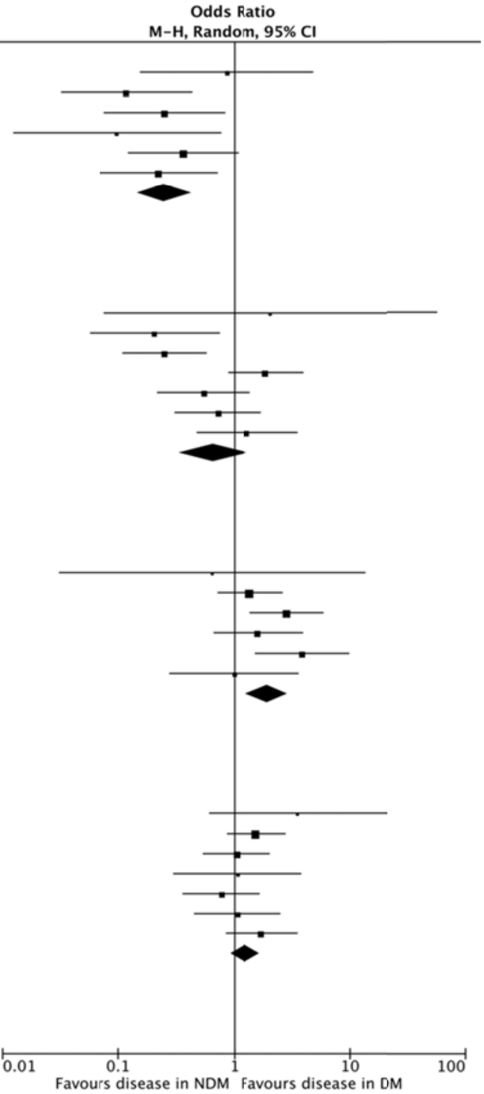

Figure 2: Forest plot comparing the presence of arterial disease by arterial segment in patients with diabetes compared to patients without.

Table 1: Demographics of studies included in the review.

Author	Age (Mean ± SD)		Gender (♂/♀)		Smoking status (smokers/non-smokers)	
	DM	NDM	DM	NDM	DM	NDM
De Bakey ME[14,a]	16-37[b]		4/2	25/16	2/4	29/12
Haimovici H[19]	-	-	-	-	-	-
Ciavarella A[20]	65 ± 9	64 ± 10	62/27	44/17	45/44	52/9
Hansen ME[15,a]	43.4 ± 5.8		29/30		45/14	
Kroger K[16]	61 ± 13		85/47		-	-
Haltmayer M[12]	66.4 (57.9-74.4)[c]	63.9 (59.5-68.7)[c]	80/26	32/21	48/58	7/45
Lazaris AM[21]	78.5 (42-92[b])		53/46		21/19	47/25
Rueda CA[25]	66 ± 12		302/148		-	-
Diehm N[23]	70 ± 11		1583/1076		1144/1515	
Ozkan U[18]	62 ± 11		538/88		494/132	
Menzoian JO[22]	67 ± 1.2/69.8 ± 1.6[d]	64 ± 1/75.4 ± 1.3[d]	-	-	73/42	98/21
Jude EB[24]	63.83 ± 10.4	65.3 ± 11.11	34/24	47/31	47/11	60/18
van der Feen C[13]	65.5 ± 13.6	65.7 ± 12.7	20/17	20/17	12/25	12/25
Diehm N[11]	74.2 ± 10.3	77.4 ± 9.6	10/15	12/13	11/14	9/16

[a]Deliberately selected young age group, [b]age range, [c]Median (IQR), [d]Smokers/non-smokers

Table 2: Characteristics of included studies

Author	Year	Country	Study design	Patients	Groups	Method of describing pattern
Proportions						
De Bakey ME[14]	1964	USA	Cross-sectional study	Patients with occlusive disease of the lower extremities	DM=6 NDM = 41	A-I, F-P, A-I/F-P, PEA/tib, F-P/PEA/tib, A-I/F-P/PEA/tib, ML
Haimovici H[19]	1967	USA	Cross-sectional study	Patients with arteriosclerosis obliterans	DM=91 NDM=98	A-I, F-P, F-P/tib, P-tib, P, tib, ML
Ciavarella A[20]	1993	Italy	Cross-sectional study	Patients with symptomatic PAD	DM=89 NDM=61	A-I, F-P, tib, F-P/tib, ATA, PTA, PEA, DP, Plant, ML
Hansen ME[15]	1995	USA	Cross-sectional study	Patients with symptomatic PAD	DM=22 NDM=37	A-I, F-P/tib, ML
Kroger K[16]	2000	Germany	Cross-sectional study	Patients with PAD	DM=46 NDM=86	A-I, F-P, tib, ML
Haltmayer M[12]	2001	Austria	Case-control study	Patients with symptomatic PAD	DM=41 NDM=65	A-I, F-P, tib,
Lazaris AM[21]	2004	UK	Cross-sectional study	Patients undergoing sub-intimal angioplasty	DM=33 NDM=66	F, F-P, F-P-tib, P-tib, tib, ML
Rueda CA[25]	2008	USA	Cross-sectional study	Patients undergoing infrainguinal revascularisation	DM=262 NDM=168	A-I, F, P-tib, ML
Diehm [N23,a]	2006	Switzerland	Cross-sectional study	Patients undergoing endovascular therapy of lower limb	DM=891 NDM=1768	I, F-P, tib

Ozkan [U18,a]	2009	Turkey	Cross-sectional study	Patients with PAD	DM=261 NDM=365	A-I, F-P, tib, ML
Scores						
Menzoian JO[22]	1989	1989	Cross-sectional study	Patients with PAD	DM=115 NDM=119	ATA, PTA, PEA, Plant
Jude EB[24]	2001	UK	Cross-sectional study	Patients undergoing infrainguinal revascularisation	DM=58 NDM=78	Individual vessels I to tib
van der Feen C[13]	2002	Netherlands	Case-control study	Patients with symptomatic PAD	DM=37 NDM=37	I-F, P-tib
Diehm N[11]	2008	Switzerland	Cohort study	Patients undergoing angiography for chronic lower limb ischaemia	DM= 25 NDM=25	Individual vessels TPT to tib, TPT-tib average score, Plant

[a]Not included in meta-analysis. A=Aorta, I-Iliacs, F=Femoral, P=Popliteal, tib=Tibials, PEA=Peroneal, ATA=Anterior tibial artery, PTA=Posterior tibial artery, Plant=Plantar vessels, TPT= Tibeo- peroneal trunk, ML=Multi-level disease

Table 3: Bollinger scoring system

Location	Occlusion	Stenosis >50%	Stenosis ≤ 50%	Plaques ≤ 25%
Single	-	4	2	1
Multiple ≤ half	13	5	3	2
Multiple > half	15	6	4	3

Adapted from Bollinger *et al* 1981. Each arterial segment will have an additive score based on the above scoring matrix. To avoid inadequate scoring the following rules should be obeyed. 1) In the presence of occlusions, plaques or stenosis are not considered. 2) When both categories of stenosis (>50% and ≤50%) are present plaques are not scored. 3) For each type of occlusive lesion only one length category is indicated